Distinct efficacy of postoperative radiotherapy in patients with resected pathological Stage IIIA-N2 lung squamous cell carcinoma

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Abstract

Background. The beneficial effect of postoperative radiotherapy (PORT) on resected pathological IIIA-N2 (pIIIA-N2) non-small cell lung cancer (NSCLC) has been a subject of interest with controversy. The aim of this study was to distinguish the clinical efficacy of PORT on lung adenocarcinoma (LADC) and squamous cell carcinoma (LSCC) among pIIIA-N2 NSCLC.

Methods. Between October 2010 and September 2016, 288 consecutive patients with resected pIIIA-N2 NSCLC at Beijing Chest Hospital were retrospectively analyzed. There were 194 cases of adenocarcinoma (ADC), 85 cases of squamous cell carcinoma (SCC), 5 cases of large cell carcinoma, 3 cases of adenosquamous carcinoma, and 1 case of clear cell carcinoma. In pIIIA-N2 LADC and LSCC 42 and 19 cases received PORT, respectively. Life Table was used for univariable analyses of factors affecting the rate of overall survival (OS), locoregional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS). Multivariable Cox proportional hazard models were used to evaluate risk factors affecting OS, LRFS and DMFS.

Results. In 194 cases of pIIIA-N2 LADC, smoking index (SI) < 400 ($p = .000$), a lower number of positive nodes ($p = .009$), a single N2 station ($p = .012$) and treatment with postoperative adjuvant chemotherapy (POCT) ($p = .006$) were independent prognostic factors for OS in multivariable analyses. Other beneficial factors included the use of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) or anaplastic lymphoma kinase (ALK) inhibitors in univariable analyses. PORT failed to show benefit in prolonging the OS of pIIIA-N2 LADC patients. In contrast, in 85 cases of pIIIA-N2 LSCC, PORT alone was a significant positive prognostic factor for OS ($p = .027$), LRFS ($p = .014$) and DMFS ($p = .030$) in multivariable analyses. Stratified analysis revealed older age (≥ 65 years) ($p = .031$) and lower T stage ($p = .042$) as predictors of longer OS in PORT group patients of pIIIA-N2 LSCC.

Conclusions. Our analysis singled out pIIIA-N2 LSCC as a NSCLC sub population who benefited from PORT, which did not show effect on the OS in pIIIA-N2 LADC. Therefore, pIIIA-N2 LSCC represents a unique cohort among pIIIA-N2 NSCLC and should be considered as an independent patient group with strong indication for PORT.

Introduction

Lung cancer is the leading cause of cancer related deaths worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for 80–85% of all cases of lung cancer. Surgery remains the most important treatment for stage I/II and IIIA NSCLC. In particular, patients with IIIA-N2 disease require surgery and supplementary treatments to improve the prognosis [2]. However, after adjuvant chemotherapy, this patient population still had a high loco-regional recurrence rate of up to 40% [3, 4]. Therefore, postoperative radiotherapy (PORT) has been incorporated into multidisciplinary management in hope that it may reduce local-regional recurrences. Nevertheless, due to lack of phase III randomized clinical trials (RCTs) [5, 6] to evaluate the effect of PORT on resected pathological IIIA-N2 (pIIIA-N2) NSCLC, its benefit remains unclear and even controversial. In many retrospective studies [7–9], the efficacy of PORT was analyzed under the general

population of pIIIA-N2 NSCLC (without separation of histologic subtypes), that may undermine the benefit for certain patient subpopulations. Lung adenocarcinoma (LADC) and squamous cell carcinoma (LSCC) are the most frequent histologic subtypes of NSCLC, accounting for 50% and 30% of all cases, respectively [10]. During the past decades, LADC had received treatments consisting of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and anaplastic lymphoma kinase (ALK) inhibitors with improved prognosis [11]. Unfortunately these inhibitors did not show the therapeutic effect on LSCC [12, 13]. Since LSCC had a higher local recurrent rate (21% vs. 14%) and lower distant metastatic rate (7% vs. 11%) than LADC in patients with resected NSCLC [14], more rigorous local treatment using PORT to eradicate micro-residues of the tumor may achieve improvement in OS in patients with LSCC [9]. These observations prompted us to analyze stage pIIIA-N2 LADC and LSCC during the period of October 2010 through September 2016, with emphasis on the effect of PORT on the outcome of patients. Our result singled out pIIIA-N2 LSCC as a unique patient population who clearly benefited from PORT.

Materials And Methods

Patients

Between October 2010 and September 2016, 288 consecutive patients with pathologically confirmed stage IIIA-N2 NSCLC (according to the 8th edition of the Union for International Cancer Control [UICC]/American Joint Committee on Cancer [AJCC] classification of tumor–node–metastasis (TNM)). Patients survived 4 months after radical resection in Beijing Chest Hospital were enrolled in this study. The medical records and follow-up data of the patients were retrospectively analyzed, including: gender, age, smoking index, histology, pathological TNM stage, types of surgery, types of N2 (N2a1 N2a2, N2b), number of positive nodes, percentage of positive nodes, number of N2 stations, postoperative adjuvant chemotherapy (POCT), PORT, postoperative adjuvant EGFR TKIs or ALK inhibitors, patterns and times of recurrence, salvage treatments, and survival status.

Surgery

The surgical methods of 288 patients were divided into thoracic surgery (261 cases) and thoracoscopic surgery (27 cases). Types of surgery contained single lobectomy (212 cases), compound lobectomy (18 cases), sleeve resection (12 cases), and total lung resection (pneumonectomy, 46 cases). Single lobectomy, compound lobectomy and sleeve resection were classified as lobectomy in data analysis. Complete mediastinal lymph node dissection or systematic mediastinal lymph node sampling was performed during surgery, with an average removal of 20 nodes per patient.

Chemotherapy

POCT was administered with a cisplatin- or carboplatin- based regimen, with a median of four cycles. A total of 38 patients did not receive POCT due to asthenia, refusal, or choice by the physician.

Therapy with EGFR TKIs or ALK inhibitors

Among 194 cases of LADC, 75 patients received therapy with EGFR TKIs or ALK inhibitors (5 patients with ALK inhibitors and 70 with EGFR TKIs). The inhibitors were given to 8 patients as adjuvant therapy after surgery and to 67 patients after tumor relapse.

Radiotherapy (PORT)

PORT was performed in 42 of 194 LADC patients and 19 of 85 LSCC patients. The administration of PORT was based on the radiation oncologists' decision or surgeon's referral. Extensive mediastinal lymph node involvement was the main indication for PORT. Techniques included three-dimensional conformal radiotherapy (3D-CRT, 21 cases) and intensity modulated radiotherapy (IMRT, 40 cases). Clinical target volume (CTV) included surgical margin, ipsilateral hilum, and high-risk ipsilateral mediastinal drainage lymph area. The planning target volume (PTV) was defined as the CTV plus 0.5–0.8 cm margins. The therapies were administered with a linear accelerator using 6–8 MV x-ray at 180–200 cGy per fraction, 5 days per week, to an average total radiation dose of 5918 cGy. PORT was used for an average of 4.38 months after surgery.

Follow-Up

The patients were followed up every 3 months after surgery for the first 2 years and every 6–12 months thereafter. The last follow-up time was December 2019. Regular follow-up included physical examination, hematology tests, chest CT scans, ultrasound of supraclavicular region, ultrasound or CT scanning of the abdomen, and other imaging procedures based on the requirement. Treatment failures were determined by the physicians based on the available information, including clinical assessments, imaging results and/or pathological examination. Follow-up information was also obtained by telephone surveys and reviewing electronic medical records. Disease recurrence at the surgical margin, ipsilateral hilum, and/or mediastinum was considered a local-regional failure (LRF). Tumor lesion appearance at other sites, including the supraclavicular zone, contralateral hilum and distant organs, were considered distant metastasis (DM).

Data Analysis

SPSS statistical software (version 23.0; SPSS Inc., Chicago, IL) was used for the statistical analyses. Locoregional recurrence-free survival (LRFS) was defined from the day of surgery to the day of documented LRF or the last follow-up. Distant metastasis-free survival (DMFS) was defined from the day of surgery to the day of documented DM or the last follow-up. Overall survival (OS) was measured from the day of surgery to the date of death from any cause or the last follow-up. The Life Table method was used to calculate median time (MT) of OS, LRFS and DMFS. Wilcoxon test was used to analyze differences between patient groups. Multivariable Cox proportional hazard models (Forward: LR) were used to adjust for differing risk factors distributions between patient groups. A statistically significant difference was set at $p < .05$.

Results

Patient Characteristics

The postoperative results of 288 pIIIA-N2 NSCLC patients included 194 cases of LADC, 85 cases of LSCC, 3 cases of adenosquamous carcinoma, 5 cases of large cell carcinoma, and 1 case of clear cell carcinoma. There were 250 (86.8%) patients treated with POCT and 61 (21.1%) patients treated with PORT.

Univariate and multivariate analyses of different potential prognostic factors affecting OS, LRFS and DMFS among 194 LADC patients of are presented in Table 1 and Table 2. Analyses of 85 LSCC patients are summarized in Table 3 and Table 4.

Table 1

Univariate analyses of factors affecting OS, LRFS and DMFS in LADC patients (N = 194)

Characteristics	No.	OS		LRFS		DMFS	
		MT (months)	P	MT (months)	P	MT (months)	P
Gender			0.065		0.158		0.247
Female	96	58.99		54.27		25.48	
Male	98	49.38		34.99		26.52	
Age (yr)			0.443		0.503		0.792
< 65	139	55.24		47.35		24.76	
≥ 65	55	54.11		40.03		27.50	
Smoking Index			0.001**		0.001**		0.010*
< 400	127	59.58		55.75		33.92	
≥ 400	67	33.00		27.97		14.26	
Types of surgery			0.468		0.205		0.079
Lobectomy	178	55.15		47.20		26.90	
Pneumonectomy	16	49.00		27.23		11.00	
Pathologic T stage			0.182		0.081		0.008**
pT1	70	56.43		55.05		40.15	
pT2	96	57.05		42.04		27.42	
pT3	28	38.00		29.56		12.45	
Types of N2			0.005**		0.006**		0.001**
a1	46	71.71		77.74		77.39	
a2	62	53.48		40.59		29.15	

Life Table method was used to calculate median time (MT) of OS, LRFS and DMFS. Wilcoxon test was used to analyze differences between patient groups. A statistically significant difference was set at p ≤ .05, represented by "*". *: p ≤ .05. **: p < .01. Abbreviations: MT = median time, LNR = lymph node ratio, PORT = postoperative radiotherapy, POCT = postoperative chemotherapy.

b	86	40.49		35.34		15.77	
N of positive nodes			0.001**		0.001**		0.000**
1–3	87	66.65		69.32		55.80	
≥ 4	107	39.50		32.82		15.65	
LNR			0.003**		0.004**		0.000**
< 20%	80	63.93		60.64		55.45	
≥ 20%	114	42.22		37.04		17.51	
N2 stations			0.002**		0.006**		0.002**
Single	46	77.71		77.74		77.39	
Multiple	148	44.34		36.97		20.91	
POCT			0.190		0.284		0.350
No	24	42.00		27.50		17.00	
Yes	170	55.16		47.64		26.94	
PORT			0.585		0.116		0.851
No	152	54.70		40.77		29.17	
Yes	42	54.73		54.73		21.39	
Therapy of EGFR TKIs or ALK inhibitors			0.017*		0.234		0.275
No/unknown	119	40.95		35.88		26.11	
Yes	75	57.81		54.22		25.92	

Life Table method was used to calculate median time (MT) of OS, LRFS and DMFS. Wilcoxon test was used to analyze differences between patient groups. A statistically significant difference was set at $p < .05$, represented by "*". *: $p < .05$. **: $p < .01$. Abbreviations: MT = median time, LNR = lymph node ratio, PORT = postoperative radiotherapy, POCT = postoperative chemotherapy.

Table 2

Multivariate analyses of factors affecting OS, LRFS and DMFS in LADC patients (N = 194)

Characteristics	No	OS		LRFS		DMFS	
		HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Smoking Index			0.000**		0.000**		0.029*
< 400	127	0.4 (0.3–0.7)		0.4 (0.3–0.7)		0.6 (0.4–0.9)	
≥ 400	67	1		1		1	
Pathologic (T stage)							0.009**
pT1						0.4 (0.2–0.8)	
pT2						0.5 (0.3–0.8)	
pT3						1	
Number of positive nodes			0.009**		0.014*		0.000**
1–3	87	0.5 (0.3–0.8)		0.5 (0.3–0.8)		0.4 (0.2–0.6)	
≥ 4	107	1		1		1	
N2 stations			0.012*		0.021*		
Single	46	0.5 (0.2–0.8)		0.5 (0.3–0.9)			
Multiple	148	1		1			
POCT			0.006**		0.032*		
No	24	2.1 (1.2–3.7)		1.8 (1.0-3.1)			
Yes	170	1		1			

Multivariable Cox proportional hazard models (Forward: LR) were used to adjust risk factor distributions between patient groups. A statistically significant difference was set as $p < .05$, represented by "*". *: $p < .05$. **: $p < .01$. Abbreviations: POCT = postoperative chemotherapy, HR = hazard ratio, CI = confidence interval.

Table 3

Univariate analyses of factors affecting OS, LRFS and DMFS in LSCC patients (N = 85)

Characteristics	No	OS		LRFS		DMFS	
		MT (months)	P	MT (months)	P	MT (months)	P
Gender			0.363		0.509		0.451
Female	7	29.50		14.50		29.50	
Male	78	39.00		29.12		30.63	
Age (yr)			0.228		0.385		0.279
< 65	60	46.91		38.08		44.23	
≥ 65	25	28.50		25.50		26.50	
Smoking Index			0.448		0.465		0.640
< 400	18	61.70		29.00		61.00	
≥ 400	67	38.25		28.83		30.40	
Type of surgery			0.464		0.586		0.917
Lobectomy	57	46.25		28.81		29.79	
Pneumonectomy	28	31.00		30.00		30.50	
Pathologic T stage			0.568		0.542		0.312
pT1-2	56	45.86		29.75		34.72	
pT3	29	31.50		25.94		21.52	
Type of N2			0.692		0.579		0.996
a1	31	70.02		38.75		38.80	
a2	26	36.00		30.00		31.00	
b	28	38.00		22.00		22.50	
N of positive nodes			0.033*		0.114		0.481
1–3	45	56.06		45.70		44.74	
≥ 4	40	26.00		22.00		22.00	

Life Table method was used to calculate median time (MT) of OS, LRFS and DMFS. Wilcoxon test was used to analyze differences between patient groups. A statistically significant difference was set at p < .05, represented by “*”. *: p < .05. **: p < .01. Abbreviations: MT = median time, LNR = lymph node ratio, PORT = postoperative radiotherapy, POCT = postoperative chemotherapy.

LNR			0.090			0.238			0.409
< 20%	51	52.22			45.04			45.01	
≥ 20%	34	28.00			21.85			22.43	
N2 stations			0.431			0.348			0.942
Single	31	70.02			38.75			38.80	
Multiple	54	36.00			25.95			29.00	
POCT			0.256			0.168			0.505
No	13	26.50			17.50			21.50	
Yes	72	46.39			30.09			34.28	
PORT			0.047*			0.008**			0.038*
No	66	36.00			25.19			28.36	
Yes	19	102.00			102.00			102.00	

Life Table method was used to calculate median time (MT) of OS, LRFS and DMFS. Wilcoxon test was used to analyze differences between patient groups. A statistically significant difference was set at $p < .05$, represented by "*". *: $p < .05$. **: $p < .01$. Abbreviations: MT = median time, LNR = lymph node ratio, PORT = postoperative radiotherapy, POCT = postoperative chemotherapy.

Table 4

Multivariate analyses of factors affecting OS, LRFS and DMFS in LSCC patients (N = 85)

Characteristics	No	OS		LRFS		DMFS	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
N of positive nodes			0.047*				
1–3	45	0.5 (0.3–0.9)					
≥ 4	40	1					
PORT			0.027*		0.014*		0.030*
No	66	2.3 (1.0-4.9)		2.5 (1.2–5.4)		2.2 (1.0-4.8)	
Yes	19	1		1		1	

Multivariable Cox proportional hazard models (Forward: LR) were used to adjust risk factor distributions between patient groups. A statistically significant difference was set at $p < .05$, represented by "*". *: $p < .05$. **: $p < .01$. Abbreviations: PORT = postoperative radiotherapy, HR = hazard ratio, CI = confidence interval.

Stratified analysis was used to analyze 85 LSCC patients who were further divided into two groups. 19 received PORT and 66 were in the non-PORT group. Table 5 compared characteristics of patients in the PORT and non-PORT groups.

Table 5

Stratified analysis of factors affecting OS in LSCC patients with or without PORT (N = 85)

Characteristic	No	Patient Number		MST (months)		
		Non-PORT	PORT	Non-PORT	PORT	P
Gender						
Female	7	6	1	29.00	49.00	0.299
Male	78	60	18	37.00	102.00	0.090
Age (yr)						
< 65	60	47	13	48.39	45.43	0.497
≥ 65	25	19	6	25.50	102.00	0.031*
Smoking Index						
< 400	18	11	7	29.50	102.00	0.098
≥ 400	67	55	12	36.50	45.86	0.234
Type of resected						
lobectomy	57	42	15	37.00	100.00	0.095
pneumonectomy	28	24	4	31.00	102.00	0.386
Pathological T stage						
T1-2	56	46	10	36.00	94.00	0.042*
T3	29	29	9	38.00	28.50	0.357
Type of pN2						
a1	31	24	7	52.00	67.00	0.183
a2	26	20	6	31.00	102.00	0.233
b	28	22	6	30.00	94.00	0.298
N of positive nodes						
1–3	45	36	9	46.50	94.00	0.180
≥ 4	40	30	10	22.50	102.00	0.071
LNR						

Life Table method was used to calculate median time (MT) of OS. Wilcoxon test was used to analyze differences between patient groups. A statistically significant difference was set at $p < .05$, represented by "*". *: $p < .05$. Abbreviations: MT = median time, LNR = lymph node ratio, POCT = postoperative chemotherapy.

Characteristic	No	Patient Number		MST (months)		
< 20%	51	40	11	46.68	102.00	0.168
≥ 20%	34	26	8	22.50	100.00	0.135
Involved N2 stations						
Single	31	24	7	52.00	67.00	0.183
Multiple	54	42	12	31.00	45.86	0.134
POCT						
No	13	11	2	24.50	67.00	0.072
Yes	72	55	17	46.22	102.00	0.187

Life Table method was used to calculate median time (MT) of OS. Wilcoxon test was used to analyze differences between patient groups. A statistically significant difference was set at $p < .05$, represented by "*". *: $p < .05$. Abbreviations: MT = median time, LNR = lymph node ratio, POCT = postoperative chemotherapy.

Survival

Median survival time (MST) of 288 of all pIIIA-N2 NSCLC patients was 49.82 months. The 1-, 5-, and 9- year OS rates were 90%, 41%, and 21%, respectively.

LADC

The MST of 194 LADC patients was 54.77 months, with the median LRFS time 42.95 months, and the median DMFS time 26.04 months. The 1-, 5-, and 9- year OS rates were 91%, 42%, and 19%, respectively. Univariate analysis for significant positive prognostic factors for OS include smoking index (SI: number of cigarettes smoked per day × number of cigarette years) < 400 ($p = .001$), N2a1 ($p = .005$), a lower number of positive nodes ($p = .001$), a lower percentage of positive nodes ($p = .003$), a single N2 station ($p = .002$) and receiving therapy with EGFR TKIs or ALK inhibitors ($p = .017$). Patient gender, age, types of surgery, pathologic T stage, and treatment with PORT or with POCT were not prognostic factors for OS. In multivariate analysis, SI < 400 ($p = .000$), a lower number of positive nodes ($p = .009$) and a single N2 station ($p = .012$) were independent prognostic factors for OS. Treatment with POCT was an independent prognostic factor both for OS ($p = .006$) and LRFS ($p = .032$) (Fig. 1). Other factors were not significantly associated with OS.

LSCC

The MST of 85 LSCC patients was 38.75 months, with the median LRFS time 28.83 months, and the median DMFS time 30.39 months. The 1-, 5-, and 9- year OS rates were 89%, 41%, and 24%, respectively. Significant positive prognostic factors for OS by univariate analysis include a lower number of positive nodes ($p = .033$) and PORT ($p = .047$). Factors of gender, age, SI, types of surgery, pathologic T stage, types of N2, percentage of positive nodes, number of N2 stations and treatment with POCT did not affect OS. It

was note worthy that PORT was the only positive prognostic factor for LRFS (p = .008) and DMFS (p = .038). Multivariate analysis that also showed having a lower number of positive nodes (p = .047) and PORT (p = .027) were independent favorable prognostic factors for OS. Also, PORT was the only independent favorable prognostic factor for LRFS (p = .014) and DMFS (p = .030) (Fig. 2).

In order to define types of patients who benefited more from PORT, stratified analysis was used in Table 5. Life Table analysis showed that patients with older age (≥ 65 years) (p = .031) and a lower T stage (p = .042) in PORT group had longer OS. Male (p = .090), SI < 400 (p = .098), lobectomy (p = .095), treatment without POCT (p = .072) and a higher number of positive nodes (p = .071) in patients of PORT group had no statistically significant difference compared with no PORT group.

Therefore, PORT demonstrates a unique favorable prognosis value for pIIIA-N2 LSCC.

Discussion

Traditionally, although both were categorized by NSCLC, we regard LADC and LSCC as different cancers due to their distinct cells of origin, unique molecular characteristics and dissimilar clinical responses to treatment. LSCC typically originates from bronchial epithelium of larger and more proximal airways (basal cells), mostly from central lung and more closely associated with smoking and chronic inflammation [15, 16]. Patients with LSCC trend to have a lower distant recurrence-free survival (DRFS) rate than those with LADC [17]. Therefore, the main objective of the therapies for LSCC patients with a high risk of local recurrence is to eradicate potentially residual microscopic tumors with surgery, such as at the resection margin or in mediastinal node areas. In a randomized study, of 366 patients with resected pN1-N2 NSCLC [18], PORT resulted in a significantly lower locoregional recurrence rate. PORT may reduce local-regional recurrence, and was more effective for patients of resected pIIIA-N2 LSCC [19]. In a randomized study of 773 lung cancer assigned 230 patients with resected stage II or stage III LSCC have received either PORT or no adjuvant treatment. The overall recurrence rate was significantly lower with PORT in patients bearing N2 disease [20]. Also, in LSCC, driver oncogenic alterations such as EGFR [11] and ALK [12] gene rearrangements are rarely detected, and these tumors are generally chemotherapy-insensitive [21]. Our study demonstrates that pIIIA-N2 LSCC patients treated with PORT had a longer median LRFS time with prolonged OS. PORT patients in our study were randomly selected to minimize the inconsistencies indications. Therefore, the advantage of PORT for pIIIA-N2 LSCC was more convincingly illustrated. PORT also indicating a higher sensitivity of squamous cell carcinoma port in another anatomic location significantly benefit for esophagus squamous cell carcinoma after surgery [22].

LADCs are thought to originate from the bronchiolar or alveolar epithelium (Clara cells or type II pneumocytes), mainly located in the peripherally located smaller airways with glandular histology features and biomarkers consistent with an origin in the distal lung [15, 16]. The discovery of EGFR gene mutations and echinoderm microtubule-associated protein-like 4-ALK(EML4-ALK) gene rearrangement led to the development of targeted therapy [23, 24], which improved clinical outcomes in a subset of LADC patients. In our study 194 LADC cases showed improved OS by POCT (p = .006), and subsequent therapy with EGFR TKIs or ALK inhibitors further prolonged OS (p = .017) of patients with tumor recurrence. The MST was

54.77 months of pIIIA-N2 LADC patients, including that addition of EGFR-TKIs to POCT are able to prolong the OS for resected LADC among NSCLC [25]. Based on the superior disease-free survival, reduced toxicity, and improved quality of patient life, adjuvant EGFR-TKIs therapy is an ideal option for II–IIIA (N1-N2) EGFR-mutant LADC among NSCLC [26].

The results derived from our study clearly distinguish pIIIA-N2 LSCC from LADC in terms of their tissue origination, etiology, genetic characteristics and most importantly, their sensitivity to PORT. Based on insensitivity of pIIIA-N2 LADC to PORT, we consider it no-longer appropriate to collectively categorize LADC and LSCC into a vague term of NSCLC.

Conclusion

We propose that pIIIA-N2 LSCC should be singled out into a unique patient population who significantly benefited from PORT. This also calls for further studies of the effect of PORT on other stages of LSCC.

Abbreviations

NSCLC: non-small cell lung cancer; PORT: postoperative radiotherapy; RCTs: randomized clinical trials; LADC: lung adenocarcinoma; LSCC: squamous cell carcinoma; EGFR: epidermal growth factor receptor; TKIs: tyrosine kinase inhibitors; ALK: anaplastic lymphoma kinase; UICC: Union for International Cancer Control; AJCC: American Joint Committee on Cancer; TNM: tumor–node–metastasis; POCT: postoperative adjuvant chemotherapy; 3D-CRT: three-dimensional conformal radiotherapy; IMRT: intensity modulated radiotherapy; CTV: clinical target volume; PTV: planning target volume; LRF: local-regional failure; DM: distant metastasis; LRFS: locoregional recurrence-free survival; DMFS: distant metastasis-free survival; OS: overall survival; MT: median time; MST: median survival time; DRFS: distant recurrence-free survival; EML4: microtubule-associated protein-like 4.

Abbreviations

NSCLC: non-small cell lung cancer; PORT: postoperative radiotherapy; RCTs: randomized clinical trials; LADC: lung adenocarcinoma; LSCC: squamous cell carcinoma; EGFR: epidermal growth factor receptor; TKIs: tyrosine kinase inhibitors; ALK: anaplastic lymphoma kinase; UICC: Union for International Cancer Control; AJCC: American Joint Committee on Cancer; TNM: tumor–node–metastasis; POCT: postoperative adjuvant chemotherapy; 3D-CRT: three-dimensional conformal radiotherapy; IMRT: intensity modulated radiotherapy; CTV: clinical target volume; PTV: planning target volume; LRF: local-regional failure; DM: distant metastasis; LRFS: locoregional recurrence-free survival; DMFS: distant metastasis-free survival; OS: overall survival; MT: median time; MST: median survival time; DRFS: distant recurrence-free survival; EML4: microtubule-associated protein-like 4.

Declarations

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Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Authors' contributions

Baolan Li conceived and designed the study. Cuimeng Tian, Guimei Liu, Yongxiang Xu, Guangrong Xia, Tongmei Zhang and Hui Jiang collected the data. Cuimeng Tian and Baolan Li analyzed, interpreted the data and drafted the article. Ji Ming Wang, Xu Zhang, Jiaqiang Huang and Zhouguang Hui revised the paper critically. All authors approved the final version to be submitted.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The ethics committee of Academic Research Project Beijing Tuberculosis and Thoracic Tumor Research Institute/Beijing Chest Hospital, Capital Medical University has approved this study and the consents from

the participants have been waived.

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Conflict of interest

All authors declare no conflict of interest.

References

1. Siegel R-L, Miller K-D, Jemal A. Cancer statistics, 2020[J]. CA Cancer J Clin. 2020;70(1):7–30.
2. Van Schil P-E, Yogeswaran K, Hendriks J-M, et al. Advances in the use of surgery and multimodality treatment for N2 non-small cell lung cancer[J]. Expert Rev Anticancer Ther. 2017;17(6):555–61.
3. Douillard J-Y, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial[J]. Lancet Oncol. 2006;7(9):719–27.
4. Rodrigo Arriagada B, Bengt D, Ariane, et al. Cisplatin-Based Adjuvant Chemotherapy in Patients with Completely Resected Non-Small-Cell Lung Cancer[J]. The New England Journal of Medicine. 2004;350(4):351–60.
5. Pechoux CL. Role of postoperative radiotherapy in resected non-small cell lung cancer: a reassessment based on new data[J]. Oncologist. 2011;16(5):672–81.
6. Perry M-C, Kohman L-J, Bonner J-A, et al. A phase III study of surgical resection and paclitaxel/carboplatin chemotherapy with or without adjuvant radiation therapy for resected stage III non-small-cell lung cancer: Cancer and Leukemia Group B 9734[J]. Clin Lung Cancer. 2007;8(4):268–72.

7. Brandt W-S, Yan W, Leeman J-E, et al. Postoperative Radiotherapy for Surgically Resected ypN2 Non-Small Cell Lung Cancer[J]. Ann Thorac Surg. 2018;106(3):848–55.
8. Wen F, Qin Z, Xiao-Long Fu, et al. The emerging outcome of postoperative radiotherapy for stage IIIA(N2) non-small cell lung cancer patients: based on the three-dimensional conformal radiotherapy technique and institutional standard clinical target volume[J]. BMC Cancer, 2015, 15(1).
9. Dai H, Hui Z, Ji W, et al. Postoperative Radiotherapy for Resected Pathological Stage IIIA-N2 Non-Small Cell Lung Cancer: A Retrospective Study of 221 Cases from a Single Institution[J]. Oncologist. 2011;16(5):641–50.
10. Kumar V, Abbas Abul RStanley-L. Robbins basic pathology[M]. Philadelphia: Elsevier/Saunders; 2013. p. 910. -K, et al.
11. Paez J-G, Janne P-A, Lee J-C, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy[J]. Science. 2004;304(5676):1497–500.
12. Calio A, Nottegar A, Gilioli E, et al. ALK/EML4 fusion gene may be found in pure squamous carcinoma of the lung[J]. J Thorac Oncol. 2014;9(5):729–32.
13. Fang W, Zhang J, Liang W, et al. Efficacy of epidermal growth factor receptor-tyrosine kinase inhibitors for Chinese patients with squamous cell carcinoma of lung harboring EGFR mutation[J]. J Thorac Dis. 2013;5(5):585–92.
14. Varlotto J-M, Recht A, Flickinger J-C, et al. Factors associated with local and distant recurrence and survival in patients with resected nonsmall cell lung cancer[J]. Cancer. 2009;115(5):1059–69.
15. Chen Z, Hammerman FChristine-M. Peter-S, et al. Non-small-cell lung cancers: a heterogeneous set of diseases[J]. Nat Rev Cancer. 2014;14(8):535–46.
16. Davidson M-R, Gazdar A-F, Clarke B-E. The pivotal role of pathology in the management of lung cancer[J]. J Thorac Dis. 2013;5(Suppl 5):463–78.
17. Moretti L, Yu D-S, Chen H, et al. Prognostic Factors for Resected Non-Small Cell Lung Cancer with pN2 Status: Implications for Use of Postoperative Radiotherapy[J]. Oncologist. 2009;14(11):1106–15.
18. Feng Q-F, Mei W, Lian-Jun W, et al. A study of postoperative radiotherapy in patients with non–small-cell lung cancer: a randomized trial[J]. International Journal of Radiation Oncology*Biology*Physics. 2000;47(4):925–9.
19. Hui Z, Dai H, Liang J, et al. Selection of proper candidates with resected pathological stage IIIA-N2 non-small cell lung cancer for postoperative radiotherapy[J]. Thorac Cancer. 2015;6(3):346–53.
20. Effects of postoperative mediastinal radiation on. completely resected stage II and stage III epidermoid cancer of the lung[J]. N Engl J Med. 1986;315(22):1377–81.
21. Koutsoukos K. Mountzios Giannis. Novel therapies for advanced squamous cell carcinoma of the lung[J]. Future Oncol. 2016;12(5):659–67.
22. Zhao Xiao-han. Wang Duo, Wang Fang, et al. Comparison of the effect of postoperative radiotherapy with surgery alone for esophagus squamous cell carcinoma patients[J]. Medicine. 2018;97(47):e13168.

23. Manabu Soda C, Young-Lim E, Munehiro, et al. Identification of the transforming EML4–ALK fusion gene in non-small-cell lung cancer[J]. Nature. 2007;448(7153):561–6.
24. Mitsudomi T, Yasushi Y. Mutations of the epidermal growth factor receptor gene and related genes as determinants of epidermal growth factor receptor tyrosine kinase inhibitors sensitivity in lung cancer[J]. Cancer Sci. 2007;98(12):1817–24.
25. Wenjie Tang L, Xiaolin X, Xueqi, et al. EGFR inhibitors as adjuvant therapy for resected non-small cell lung cancer harboring EGFR mutations[J]. Lung Cancer, 2019, 1366–14.
26. Zhong W-Z, Qun W, Wei-Min M, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II–IIIA (N1–N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study[J]. The Lancet Oncology. 2018;19(1):139–48.

Figures

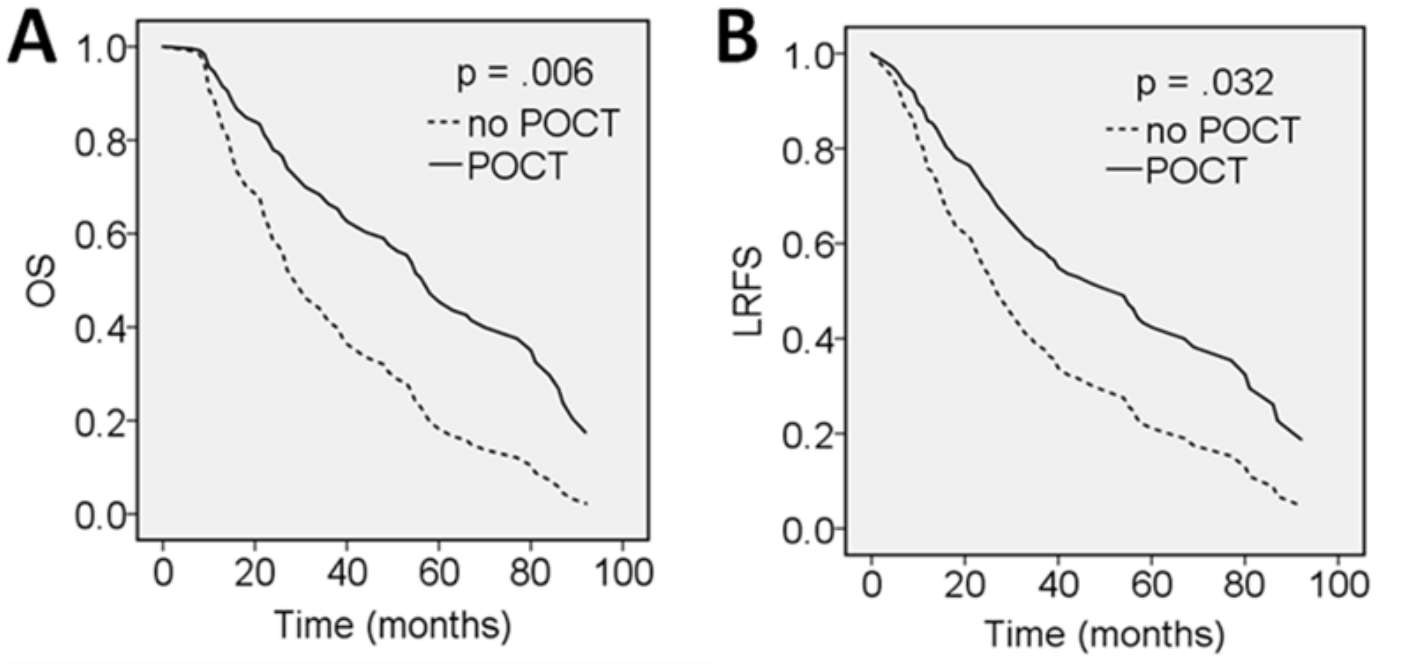

Figure 1

The effect of POCT on overall survival (OS) (A) and locoregional recurrence-free survival (LRFS) (B) of LADC patients (N = 194). Multivariable Cox proportional hazard models (Forward: LR) were used to adjust risk factor distributions between patient groups. POCT was an independent prognostic factor both for OS (p = .006, A) and LRFS (p = .032, B).

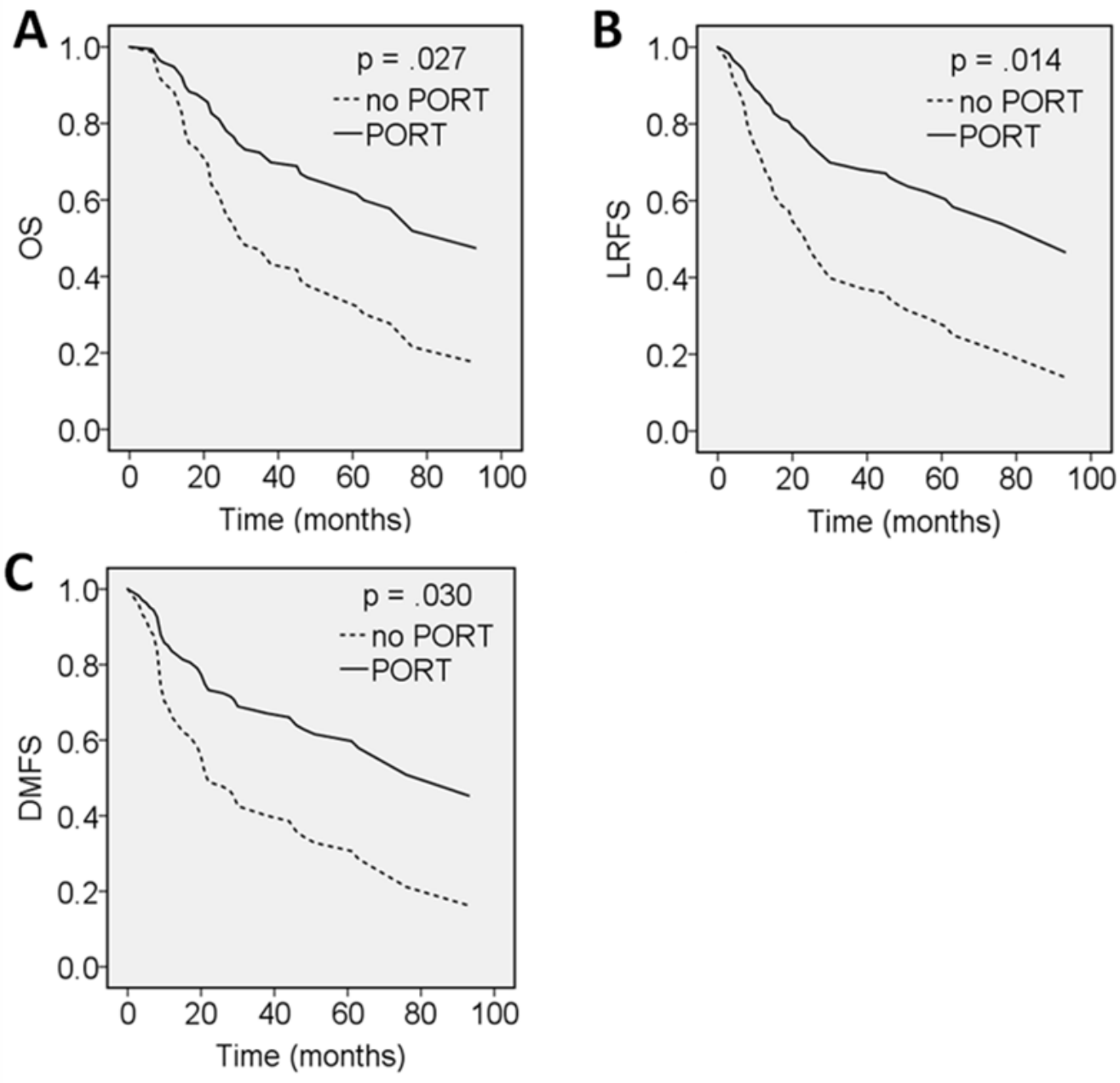

Figure 2

The effect of PORT on overall survival (OS) (A), locoregional recurrence-free survival (LRFS) (B) and distant metastasis-free survival (DMFS) (C) in LSCC patients (N = 85). Multivariable Cox proportional hazard models (Forward: LR) were used to adjust risk factor distributions between patient groups. PORT alone was a significant positive prognostic factor for OS (p = .027, A), LRFS (p = .014, B) and DMFS (p = .030, C).